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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/783,734	01/16/97	FRIEDMAN J	600-1-162CP2

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EXAMINER	
DRAPER,G	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/22/00

Please find below and/or attached an Office communication concerning this application or proceeding.

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UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	19

DATE MAILED:

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on Election of 11/99 and 7/00.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-48, 51-73 is/are pending in the application.

Of the above, claim(s) 1-28, 34-~~48~~, 51-66 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 29-33, 67-73 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims 1-48, 51-73 were ~~are~~ subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☒ Information Disclosure Statement(s) ~~PTO-1449, Paper No(s).~~ 10 & 4/98

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

★ U.S. GPO: 1996-409-290/40029

1. Part III: Detailed Office Action

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1647.

2. Formal Matters:

The title of the invention is not descriptive. A new title is required that is clearly indicative of the elected invention to which the claims are directed. The following title or the like is suggested: "OLIGONUCLEOTIDES OF THE OB-R ISOFORMS AND METHODS OF DIAGNOSING BODY WEIGHT".

The abstract also needs to be amended to make it more specific to the elected invention.

3. Restriction Requirement:

It is pointed out that applicant's traversal of the restriction and election of specie was addressed in the supplemental restriction of 1-20-00. Furthermore, the Interview of 7-21-00 further clarified the restriction and election of specie. Therefore, this office action is directed to the merits of claims 29-33 and 67-73. Claims 1-28, 34-48 and 51-66 are withdrawn from consideration as being directed to non-elected inventive groups.

The requirement is still deemed proper and is therefore made FINAL.

4. Objections and 35 USC 112 Rejections:

4a. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29-33 and 67-73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is pointed out that the claims have been presented in very poor format and constitute an improper Markush format and possibly some improper products, their fragments and fusion products claims, as well as the various method claims. In those instances where there are multiple products or methods that are presented in the improper Markush format, each of the products and

the methods are clearly patentably distinct, wherein independent or separate claims should have been presented for each of these separate products and to the separate methods. As a result and in many instances, applicant's claims are prolix because they contain long recitations or unimportant details which hide or obscure the invention, or that the recitation of very long detailed claims setting forth so many elements that invention cannot possibly reside in the combination should be rejected as prolix (such as those listed in the subparts of a, b, c, d, and subparts, like I, ii, iii, I(1), (2), etc.) that really should not appear in this format [See *Ex parte Iagan*, 1911 C.D. 10, 162 O.G. 538 (Comm'r Pat. 1910); and *In re Ludwick*, 4 F.2d 959, 1925 C.D. 306, 339 O.G. 393 (D.C. Cir 1925) respectively].

Additionally, the format of many of the claims comprise double inclusion of an element in members of a Markush groups, where there is overlapping members for alternatives recited in a claim's Markush groups, or where the claim can be read to include the same element twice [For support see *Ex parte White*, 759 O.G. 783 (Bd App 1958; *Ex parte Clark*, 174 UPSQ 40 (Bd App. 1971; *Ex parte Kristensen*, 10 USPQ2d 1701 (Bd. Pat. App. & Inter. 1989)] This causes the claims to be objectionable and indefinite.

Further, the claims represent undue multiplicity/an unreasonable number of claims or claim limitations, that are unreasonable in view of the nature and scope of applicants's invention and the state of the art, inasmuch as it relates to confusion of the issue. The Examiner recognizes that there may not be a large number of claims, but this is because applicants have chosen to combined many of these distinct products and/or limitations/embodiment into one claims. However, the issue is still the same, which makes this consistent with the CCPA's position set forth in In re Chandler, 254 F.2d 396, 117 USPQ 361 (1959) and In re Chandler, 319 F.2d 211, 225, 135 USPQ 138, 148 (1963) where it was held that applicant's latitude in stating their claims in regard to number and phraseology employed "should not be extended to sanction that degree of repetition and multiplicity which beclouds definition in a maze of confusion"). Furthermore, such claims, or claim limitations or permutations could be rejected one over the other if they differ only by subject matter old in the art (*Ex parte Whitelaw*, 1915 C.D. 18, 219 O.G. 1237 (Comm'r Pat.

1914), where this doctrine is applied when the claims are unduly multiplied or are substantial duplicates (*Ex parte Kochan*, 131 USPQ 204, 206 (Bd. App. 1961).

The claims are further rejected under 35 USC 112/2nd paragraph, because certain portions of the claims do not expressly set forth physical limitations to define the fragments, portions/pieces or Oligo's, thus, the specification has not clearly defined the metes and bounds of the claims, nor has the specification provided a written description for these protein products, or the precise make-up of these fragments and analogs. The specification fails to provide an adequate and/or specific written description for the broad products of the claims such as for fragments, functional derivatives, analogs and variants. As set forth in Reagents of the University of California v. Eli Lilly & Co. 119 F3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997), to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of the broad products of the claims such as for fragments and analogs "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, an adequate written description of a these broad protein products, requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it/making it; what is required is a description of these various protein products

themselves (at 1170, 25 USPQ2d at 1606. (page 1404). Furthermore, the name of the broad products of the claims such as for fragments, functional derivatives, analogs and variants is not itself a written description of these products; it conveys no distinguishing information concerning their identity. Accordingly, the specification does not provide a written description of the invention of claim 5. (page 1405).

Claims 29-31 and 67-72 are further indefinite, because applicants claim nucleic acids that will hybridize under "stringent" conditions. Stringent is a relative term because the stringency used in a particular process depends on variable parameters used in the process. Since those of skill in the art vary the parameters to achieve different degrees of stringency depending on their purpose, there is no standard degree of selectivity associated with the term stringent, and the term stringent alone as used in the claim does not provide sufficient guidance such that those of skill in the art can know what to make or how to identify it. See, for example, Anderson et al., §11, pages 105-107, teaching the routine variation of buffer composition and temperature, depending on the purpose at hand. If the parameters used in the instant specification are sufficient to provide selectivity that would identify the nucleic acids that Applicants intend to claim, it is suggested that the parameters sufficient to define the degree of stringency intended be stated in the claims, because limitations on general terms are not imported from the specification to the claims.

In further reference to the relative hybridization conditions, when a word of degree is used as a limitation, it is necessary to determine whether the specification provides some standard for measuring that degree. See *Seattle Box Company, Inc. V. Industrial Crating & Packing, Inc.*, 731 F.2d 818, 221 USPQ 568 (Fed. Cir. 1984). In this case, the specification does not enable one skilled in the art to reasonably establish what may be construed as being within the metes and bounds of the word of degree. Therefore, one of ordinary skill in the art would not be apprised as to the claimed invention's scope when the claims are read in light of the specification. See *Ex parte Oetiker*, 23 USPQ2d 1641.

Claim 72 is indefinite and/or confusing in its dependency from claims 67-70 and the further limitation that the nucleic acid is RNA, because all or part of the limitations in claims 67-

70 refer to nucleic acids that encodes for all or portions of the various encoded variant forms of the receptor. Thus, the limitation for RNA contradicts these limitations. Therefore, correction and/or clarification is requested. In a similar manner, claims 29b, and 31-33 are directed to complementary sequence, but this language renders the claims indefinite and confusing because the complementary sequence can not encode for the amino acid sequence, and parts "a"refers to the oligo's in terms of the encoded amino acid sequence as recited in the preamble of the claim. Therefore, this limitation should be deleted or the limitation should be amended to more clearly define what is intended. While applicants are entitled to claim complementary sequences, the claims must clearly define the complementary sequence and it should not be done in terms of an encoded amino acid sequence.

Claims 30, 67 and 69 are indefinite and/or redundant or confusing in the limitation "wherein the numbering is based on the amino acid sequence of SEQ ID NO: 50", because the other prior limitations in the claims refer to specific oligo's of specific SEQ ID. Thus, it is not clear which controls. Clarification and/or correction is requested.

Claim 29c is confusing in the recitation for hybridizable sequence of parts 29a or 29b because the preamble of the claim states that the oligo's hybridize, thus, this limitation is not further limiting.

The claims are also confusing in the manner in which the oligo's are defined in terms of the nucleic acid sequence in certain parts versus the encoded amino acid sequence in other parts or subparts of the claim. As such, it is not clear which is controlling.

The claims are indefinite, incomplete and confusing for failing to recite a point of reference for the sequence and residue numbers referred to therein. This is further confusing and contradictory from the specification which defines this in different way relative to human or murine OB-R; nor is it always exactly clear which variant form of the Ob-R this numbering represents, thus, it is not clear what the controlling meaning is for the claim interpretation. This is further complicated by the fact that the specification uses variant to mean different things throughout the specification, such as for splice variants, naturally occurring variant, or variant that are the direct result of

specific modifications. The claims should clearly have a point of reference for the numbering intended, such as by a specific Seq Id No, or with reference to a mature/native, which particular specie form (e.g. human or mouse form), wherein the form/variant/length is clearly identified. Applicants should amend the specification and claims to recite consistent terminology without introducing new matter.

4b. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29-33 and 67-73 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain variant forms of the OB-R, does not reasonably provide enablement for: a) Ob-R isoforms devoid of characterization or merely defined by abbreviations as in claims 30, 32-33, 67, 69; b) for any Ob-R merely defined by the primers of claims 3-4; and c) for any and all encoded variant OB-R isoforms as in claims 30, 67, 69; d) oligo's for the various hybridizable sequences, as in claims 29-31, 67-73; e) oligo's for complementary sequences that have been defined in terms of the encoded amino acid sequence, as in claims 29, 31-33; and e) for oligo of specific clones, as in claims 29d, 32-33. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

These various issues will be addressed herein below because the specification does not appear to be enabling for the full scope of the polypeptide of these claims. First of all it is pointed out that the Examiner concedes that the specification has provided enablement for making some of the claimed oligo's, but there is insufficient examples, evidence or guidance to enable all of the claimed products. While it is well settled that a specification need not contain examples in order to be enabling, in the express absence of such, the specification must provide enablement alternatively in the form of evidence or guidance. It is also known and accepted that examples, evidence of guidance are not required if, on its face, it is clear to the skilled artisan that the claims

are enabled; and when there is no reason to question the objective truths of applicant's mere statement of assertions that the full scope of the claimed ob polypeptide are enabled by the specification's teachings. The following are reasons for questioning the objective truth. It is further pointed out that certain aspects of this scope rejection is based on the fact that the oligo's or full length nucleic acids for the OB-R isoforms is claimed and defined in terms of the encoded amino acid sequences.

The breadth of the language of the claims for any oligo that hybridize under stringency conditions" is not commensurate in scope with the enablement provided by the specification. First of all it is pointed out that the term "hybridize" or "hybridization" generically refers to a process in which a strand of nucleic acid joins or matches up with a complementary strand through the process of base pairing, wherein the process is basically used to locate or identify nucleotides. It has been well established in the art that 15-20 bases have been considered sufficient to achieve this process; however, in some instances the conditions under which the hybridization is performed often times have an effect on the outcome. With these points in mind, then is it the examiner's position that given the claims in their broadest reasonable interpretation, this language reads on and infinite number of possible DNA sequences for which there has not been sufficient enablement.

At first glance one could assume that the hybridized oligo's sequence encodes for the various OB receptor that has the sequence of the various Seq ID; however, the scope of the s hybridizable DNA sequence **does not** have to be related to the OB receptor has the amino acid sequence of any of the Seq ID, but rather it only has to join-up and be complementary to a nucleic acid of the various Seq ID. Initially the process of hybridization was concerned with the joining of DNA sequences from genetically different specie; however, as written the claims are not limited to DNA sequences from different species, nor are they restricted to mammalian forms. Rather, in addition to the specie forms of the oligo's, this language encompasses: 1) oligo sequences that are the result of degeneracy; 2) oligo sequences that encode for biologically active Ob receptor; 3) oligo sequences that **do not** encode for biologically active OB receptor; 4) oligo sequences that

encode for any number of fragments or derivative, or analog of the Ob receptor; 5) oligo sequences that encode for Ob- receptors that are the result of deletions, insertions; additions; and modified forms of the receptor, such as allelic variants or post-translationally modified forms of the receptor.

Although the specification and claims recite this language per se (i.e. for oligo sequences that hybridize), the working examples do not provide examples or a representative number of different sequences for the entire scope of the claims that would enable all of the above oligo sequences with assurances that they possess the **desired** characteristic. The mere recitation of this term, and the definitions provided do not serve as sufficient guidance, in the absence of a representative number or examples, to enable the breadth of the claims for the various oligo sequences as has been exemplified above (See Ex parte Forman, 230 USPQ 546). Since the first paragraph of the statute under 35 USC 112 requires that there must an enabling disclosure to support the breadth of the claims, a review of the specification confirms that the scope of the various oligo sequences that have been exemplified above have not been enabled; and in the absence of sufficient guidance, it would require undue experimentation (see Ex parte Forman, supra) to enable all of the sequences that are encompassed by the claims.

Relative to certain portions of the claims, the specification is not commensurate in scope for the claimed oligo's and methods of using such wherein the Ob-R isoforms are merely referred to by a name, or very limited characterization without the recitation of any other identifying or fingerprinting characteristic-physically or functionally. While some of the claims refer to specific Ob-R isoforms by the specific SEQ ID, the various parts and subparts do not define such. Some of the claims refer to the receptor by a name, but fails to set forth any physical characteristics (MW and how it is determine, the amino acid composition or sequence, pI, or other finger-printing characteristics), or specific or non-specific functional/biological activity, nor does it require a homogeneous or purified protein. A name or an abbreviation is arbitrarily assigned by the researcher who isolates or discovers the protein based on the activity they have associated with it, however, as is the case with most proteins, there are generally many activities associated

with a protein, and any one scientist will assign a name to a protein based on the particular activity that they are researching. This often leads to confusion in the art about what protein is actually being referred to as compared to other proteins with the same physical features, and it also results in any one protein being given/assigned different or multiple names, even though the resulting protein per se is the same despite the various names assigned to it. This is especially true for new and novel proteins, because names are subject to change, as has been the case for many protein, especially for many of the cytokines. In fact the abbreviation the Ob-r protein is also referred to as leptin-receptor. Therefore, a name, without any identifying characteristics, as with claim 1 which does not even recite any functional characteristics, does not serve to sufficiently distinguish or define the features of a protein so as to enable the skilled artisan to know what is encompassed and intended by such in order to practice the claimed invention. This is further complicated by the fact that there are often multiple or variant forms of a protein, such that without specifically define characteristics, the skilled artisan would not know how to obtain the proper protein. The failure of the claim specifically claim the receptor by characterizing in the instant case is further complicated by the fact that the art has shown that there are multiple forms of the OB-R, which the size of these variant forms differ drastically, despite some homology in a large portion of the receptor at the extracellular, transmembrane and intracellular domains. In a similar manner, claims 3-4 are not enabled for the full scope of Ob-r that can be identified by the small primer sequences. These claims read on variant forms as well as modified forms of the receptor.

The claims are also non-enabling for failing to define the point of reference of the numbering of the amino acid residues, and therefore, are not enabled for all OB-r the have the designated number of residues. By merely referring to the number of amino acids that the protein has without specifying to nature or make-up of these specific nucleic acid sequence or the encoded amino acid sequences. However, the specification is not enabled form such, and the skilled artisan would encounter undue experimentation for trying to determine the make-up of the protein that would have this wide range of amino acid residues-especially in the absence of the claims to recite biological activity.

Furthermore, there is no broad based enablement for generating the various potential encoded OB-R variants, particularly since the claims do not require that the variants possess a specific "biological activity". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, absent a sufficient number of examples; or evidence or sufficient guidance; or in the absence of a reproducible and/or predictable functional assay; or in the absence of concrete structure/function studies to guide the skilled artisan to amino acid residues or regions where such modification could be made on the encoded Ob-R protein with reasonable assurance that the resulting variant or oligo that corresponds analogs will possess the desired activity.

In further reference to variants, hybridizable sequences, and mere reference to the Ob-R isoforms merely by the name, the following is an overview of information provided in the specification that applicants appear to be relying upon to enable the breadth of the claims. The specification refers to analogs of the Ob polypeptide that result from substitutions and possibly deletions at the divergent/non-conservative sites between the mouse and human protein. Further, these substitutions refer to a comparison between the human and mouse forms of the protein, but the claims are not limited to these two specie forms, thus, it is not clear how such divergence and modification are determined when other specie forms are involved (e.g. is the other specie form compared to human or mouse in order to determined divergent sites for possible modification). Applicants simply state that the modifications can be made and the resulting analog can be tested to determine its activity. There are no binding studies to determine binding sites which represent potential sites for modification to obtain both agonist and antagonist or for oligo's that would be used in the methods as claimed. Without binding studies, the skilled artisan would be faced with undue experimentation for trying to determine if a particular oligo, or encoded analog or variants possessed the same binding and that would be able to hybridize for the detection of body weight abnormalities. The generation of any type of oligo's or variants and analogs may not be considered undue experimentation if there is some guidance, in the absence of sufficient examples,

that limits the specific location and type of modifications, as well as involves a routine screening procedure. See Ex parte Mark 12 USPQ 2d 1904 (Bd. Of Pat. App. and Inter. 1989). In this regard, not only is there not sufficient examples to enable the breadth of the claims, but the guidance give is also not sufficient because all that applicants have provided is mere sequence information about the protein and limited biological activity studies, and places where there is divergence between the human and mouse sequences.

While it is conceivable that conservative substitutions do not materially affect the structure and function of a protein, this is not always true. It would, however, appear that the specification may be enabled for conservative substitutions, but the claims are not limited to such, but instead encompass agonist as well as antagonist, but the is insufficient guidance for obtaining receptor variants that possess the full scope of the modification of the claims. There is no guidance given as to the composition of the various variants and analogs that would function as a ob-r protein as broadly claimed, and no assay taught for screening the functioning analogs from the non-functioning analogs. The claims are not enabled by the specification as filed because they embraces an undeterminable number of embodiments and variations which are not directly supported by the specification and testable in a screening assay. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structural/ functional relationship, e.g. such as various sites or regions where the biological activity resides or regions directly involved in binding, stability, or catalysis; and in providing the correct three-dimensional spatial orientation for biologically active or binding sites, or for sites which represent other characteristics/properties of the protein. These or other regions may also be critical determinants of antigenicity. These various regions can tolerate only relatively conservative substitutions or no substitutions, however, Applicant has provided little or no guidance beyond

the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions, insertions or deletions), and the nature and extent of the changes that can be made in these positions in order to obtain the various ob analogs. Such a definition might also read on previously characterized proteins, or alternatively, might include proteins with additional functions or activities neither envisioned nor enabled by applicants in the current invention. See Ex parte Forman, 230 U.S.P.Q. 546 (BPAI 1986) with regard to the issue raised above and In re Fisher, 166 USPQ 18.

There are no specific teachings for what kind or the nature or extent of what the specific substitutions, deletions or additions would have to be in order for the resulting protein to have the same activity as the ob-r protein. And although the claims state that the protein must have the recited property, in the absence of the specification to teach and enable structure/function studies on the protein, the skilled artisan would have the resort to a substantial amount of undue experimentation in order to determine which amino acids would be substituted, added or deleted while still maintaining the desired biological activity. Further, the cited portion of the specification only provide "boiler-plate" citations for modification on proteins in general, but has not shown how to specifically extrapolate this to ob, therefore, this constitute inadequate guidance for the vast number of analogs/mutants that are encompassed by the claims, and is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The scope of applicant's claims encompass modification on the protein that would be critical as well as non-critical for the biological activity of the protein. Thus, even if critical residues were identified, which in this case they are not, the mere identification of these critical regions would not be sufficient as the ordinary artisan would immediately recognize that the modified site must assume the proper three-dimensional configuration to be active-which conformation is dependent upon surrounding residues. The substitution/insertion/ deletion of non-essential residues can often destroy activity, therefore, it is deemed that to make each of the possible amino acid modifications for each of the non-essential residues, even if only conservative

replacements were made, would also constitute undue experimentation. The introduction of non-conservative substitution, non-naturally occurring amino acids, deletions or insertions further raises the possible number of species. This is applicable for the various oligo's of the claims Therefore, Applicants have not presented enablement commensurate in scope with the claims.

As stated above, the specification is not enabling for complementary sequences of claims 29b, and 31-33, which encodes for all or portions of the Ob -R isoforms, because the complement can not do this. Amending the claims to delete reference to the encoded protein, or the cancellation of complement portion of claim 29, or presenting proper complement claims as suggested above would obviate this portion of the rejection. Also similar to the above, the claims are not enabled claim 72 for RNA sequences, which depend from claims which define the oligo's in terms of the encoded amino acid sequences.

Finally, claims for oligo of specific clones, as in claims 29d, 32-33 require for practicing the claimed invention must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. When biological material is required to practice an invention, and if it is not so obtainable or available, the enablement requirements of 35 USC §112, first paragraph, may be satisfied by a deposit of the material. See 37 CFR 1.802.

The specification does not provide a repeatable method for obtaining the clones and the various oligo's from such, and it does not appear to be a readily available material. Therefore, Deposit of these various clones would satisfy the requirements of 35 USC §112, first paragraph.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or Declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent;

(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803-1.809 for additional explanation of these requirements.

Therefore, the claims should be amended to recite the deposit numbers for the various clones. Further, applicants must provide a copy of the contract for such deposits, with all of the necessary averments for such.

5. Prior Art Rejections:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor

and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5a. Claims 29-33 are rejected under 35 U.S.C. 102 as being anticipated by Tartaglia et al (`621).

First of all, it is pointed out that the claims are directed to various MARKUSH groups for the claimed embodiment, thus, only one element of the claim has to be met to support the various rejections. Therefore, the art will be applied accordingly.

No one claim is specifically directed to a single oligo, nor a single form of the Ob-R, thus, the part art is applied in the broadest sense. Furthermore, the art anticipates at least certain portions of the claims for allelic variants, hybridizable oligo's , subparts, based on the following teachings.

Tartaglia et al disclose the cloning of the human and mouse OB-R. The nucleic acid and amino acid sequence for both human and mouse OB-R has been compared and both contain the WSX motif consistent with other Class I cytokine receptors. The patentee also discloses variant forms of the Ob-R, the preparation of oligo, and the use of such in diagnostic methods (see the Seq ID and claims). Also taught is that the cloning of this receptor will provide understanding in the mechanism of leptin action and provides important implications for understanding body weight dysfunctions and the treatment/regulation of such, and that various oligo's can be prepared for use in the various diagnostic method for disorders/diseases that are associated with or modulated by the variant OB-Receptors. The teachings for the existence of splice variants provide clear motivation for the skilled artisan to use the DNA to probe a genomic library to obtain variant forms of the receptor (See Ex parte Anderson, 30 USPQ d. 1867)-thus, rendering obvious the instant claims that recite a DNA sequence that is different from that disclosed in the prior art.

5b. Claims 29-33 are rejected under 35 U.S.C. 102 as being anticipated by, or in the alternative under 35 U.S.C. 103(a) as obvious over Snodgrass et al (`748, `211, `610, `123 or `098).

Each Snodgrass et al disclose a novel hematopoietin receptor having a WSX motif and having sequence homology to other hematopoietin receptors such as the Il-6R, wherein this receptor was detected in various human tissue. The initial patents by Snodgrass et al was not aware of the fact that their hematopoietin receptor was one of the variant forms of the Ob-Receptor, however, the receptor of Snodgrass et al is now known as one form of the Ob/leptin receptor (see the claims). In the `748 patent, the detection of two different sizes of mRNAs suggested the presence of homologous genes or alternative splicing (col 15). At col 2. Lines 57-59, and col 10 it is taught that this receptor can be used to screen for a ligand; further taught is that the receptor can be used to cause cellular proliferation or differentiation (col 13), additionally taught at col 12-14 is the preparation and use of antisense an ribozymes for use to inhibit translation of the receptor and the use of the DNA to diagnose for disease resulting from aberrant expression of the receptor; and that the receptor can be used for the production of antibodies, agonist and antagonist (col 6 & 10). At col 5 it is taught that altered forms of the DNA can be prepared and used; and that the receptor can be expressed using various prokaryotic and eukaryotic cells with the aid of various regulatory sequences (col 6-10). Further taught at col 5 lines 34-45 and at col 10 is that the receptor can be ligated to heterologous sequences to produce fusion protein or chimeric proteins, in which the receptor can be fused to an antibody.

While the Snodgrass et al patent, `748 did not expressly disclose the identity of the ligand as the ob/leptin protein or that their receptor was one form of the ob/leptin receptor, in view of the fact that the receptor has been identified as a hematopoietin receptor and in view of the fact that the instant receptor has a WSX motif and belongs to the family of hematopoietin receptors, despite the difference in what the receptor is referred to by their different names, the receptor protein per se and the DNA encoding it or the specific oligo's would appear to be the same and is therefore anticipated by the art [See In re Best, 195 USPQ 430, and In re Swinehart, 169 USPQ 226)]and the burden is upon applicants to establish a patentable difference. As stated above, although the prior art does not refer to their receptor as the ob/leptin receptor, and does not expressly teach alternative or variant forms, at col 4, line 20-23 it is stated that multiple libraries

may have to been screened for a full length cDNA. In view of the fact that it has been well established that many cytokines have multiple forms of the receptor as well as variant of some of the forms of the receptors (this is especially true for many cytokines and the hematopoietins), the teachings at col 15 in conjunction with the teachings at col 4 lines 19-39 provide clear motivation for the skilled artisan to use the DNA to probe a genomic library to obtain variant forms of the receptor (See Ex parte Anderson, 30 USPQ d. 1867)-thus, rendering obvious the instant claims that recite a DNA sequence that is different from that disclosed in the prior art.

However, each of the subsequent patents to Snodgrass et al disclosed nucleic acids for the variant forms of their hematopoietin receptor, and that oligo's could be made from such and used diagnostically.

5c. Claims 67-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tartaglia et al (621) or Snodgrass et al (`123 or `098).

The disclosure of the prior art has been set forth above. Additionally, each of Snodgrass et al set forth methods for either detecting leptin variants or detecting the leptin receptor(s) in other tissues (see the claims). Although the prior art does not set forth diagnostic methods in a manner exactly as claimed, the various diagnostic methods, the obvious teachings for preparing oligo's, and applicant's broad claims and the use of open-ended claim's language and the hybridizable language would have rended the claims prima facie obvious.

7. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The other prior art listed on the 892 is cited as of interest to show related art.

9. Advisory Information:

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to **Garnette D. Draper, Art Unit 1647, whose telephone number is (703) 308-4232.** Examiner Draper can normally be reached Monday through Friday, 9:30 A.M. to 6:00 P.M.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices

published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. **NO DUPLICATE COPIES SHOULD BE SUBMITTED** so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. **Please** advise the Examiner at the telephone number above when an informal fax is being transmitted.

GARNETTE D. DRAPER
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GROUP 1800